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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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Asthma is associated with lower respiratory tract involvement and worse clinical score in children with COVID-19

To the Editor,

During the SARS-CoV-2 pandemic, most clinical reports about COVID-19 manifestations and risk factors have been focused on adults, while data on children are relatively limited. COVID-19 mortality in children is considerably lower than in adults, and children are considered at lower risk for severe respiratory manifestations of the disease.[1]

Asthma is one of the most prevalent chronic conditions in children and is also a frequently reported comorbidity among children with COVID-19.[2,3] Despite that, the relationship between asthma and COVID-19 in children is not fully understood, as data regarding this relationship are mainly from adults.[4]

The objectives of this study were to describe the involvement of the lower respiratory tract (LRT) in children and adolescents with COVID-19 and to examine the relationship between asthma and the manifestations and severity of COVID-19.

This is a cross-sectional, retrospective, and observational study. Clinical data were collected from medical records of children and adolescents (0 to <18 years) seen in the emergency room (ER) of Sabará Hospital Infantil (São Paulo, Brazil) between March 2020 and January 2021 who had a diagnosis of COVID-19. Cases were defined by a clinical diagnosis of COVID-19 supported by a positive RT-qPCR test for SARS-CoV-2. The severity of cases (maximal level of the illness) was classified into mild, moderate, severe, or critical (Table 1 of the Supplementary Appendix S1).[5] The presence of comorbidities was recorded according to family information. Younger children (≤5 years) with recurrent wheezing were considered as asthmatic children for the analysis. LRT involvement was defined by the presence of any of the following: dyspnea; wheezing; respiratory distress; SpO_2<93%; SABA (short-acting beta-2 agonist); or oxygen (O_2) use. The study was approved by the Research Ethics Committee of the institution.

In total, 607 children and adolescents were diagnosed clinically with COVID-19, but 19 were excluded from the study due to the diagnosis being established only by serology or having incomplete data.

Among the 588 included children, 56.0% were boys. The median age was three years (IQR = 1–8 years). Eight-five (14.5%) children were hospitalized, 28 (4.8%) in ICU. A relevant comorbidity was reported in 157 (26.7%) cases, including asthma (12.2%), other allergic diseases (7.0%), neurological disease (6.5%), and prematurity (3.9%).

Fever (67.5%) and nasal discharge/congestion (55.4%) were the most frequently reported symptoms, and LRT involvement was observed in 14.3% of the cases. Regarding illness severity, 88.2% of the children were classified as mild. There were no deaths.

Asthmatic children were older than non-asthmatic children (5 [3–10] years vs 3 [1–8] years, $p < .001$). Some demographic and clinical data of asthmatic and non-asthmatic children are shown in Table 2 of the Supplementary Appendix S1. LRT involvement, dyspnea, wheezing, respiratory distress, SABA use, and SpO_2<93% were each significantly more common among asthmatic children (Table 1). Abnormal chest radiography was found in 17.1% (7 in 41) of children with asthma and in 16.2% (27 in 167) of those without asthma ($p = .87$). Asthma was significantly associated with COVID-19 severity score (Table 1).

In multivariate analysis, LRT involvement was significantly associated with prematurity and asthma, whereas a more severe

TABLE 1 Main lower respiratory symptoms and signs and some COVID-19 outcomes in children and adolescents with and without asthma

	Total group (*N* = 588)	Asthma (*N* = 72)		No asthma (*N* = 516)		
Symptom/signs	**%**	***N***	**%**	***N***	**%**	**p**
Cough	44.0	41	56.9	218	42.2	.02
Dyspnea	9.0	15	20.8	38	7.4	.001
Respiratory distress*	7.5	16	22.2	28	5.4	<.001
Wheezing	4.8	14	19.4	14	2.7	<.001
LRT involvement**	14.3	28	38.9	56	10.9	<.001
SABA use	7.1	23	31.9	19	3.7	<.001
SpO2<93%	4.6	8	11.1	19	3.7	.01
Use of O_2	4.3	3	4.2	22	4.3	.9
Hospitalization	14.5	8	11.1	77	14.9	.48
ICU	4.8	4	5.6	24	4.7	.77
Use of antibiotics	13.6	14	19.4	66	12.8	.14
COVID-19 severity score[c]						
Mild	88.2	54	75.0	465	90.1	<.001
Moderate	1.4	1	1.4	7	1.4	
Severe	7.3	16	22.2	27	5.2	
Critical	3.1	1	1.4	17	3.3	

*chest retraction and/or subcostal retraction and/or tachypnea in the absence of fever.; **dyspnea and/or wheezing and/or respiratory distress and/or SpO_2<93% and/or SABA use and/or use of O_2.

TABLE 2 Variables significantly associated with lower respiratory tract (LRT) involvement and more severe clinical score during COVID-19 infection in children and adolescents by multivariate analysis

Variable	OR	95% CI	p
LRT involvement			
Prematurity	4.44	1.8 – 11.3	.002
Asthma/recurrent wheezing	5.23	2.9 – 9.5	<.001
More severe COVID-19 (moderate or severe score)			
Infant	2.64	1.5 – 4.8	.001
Asthma/recurrent wheezing	3.56	1.8 – 7.2	<.001
Neurological disease	3.81	1.6 – 9.1	.002
Prematurity	7.65	3.0 – 19.5	<.001
Hospitalization			
Infant	2.75	1.6 – 4.7	<.001
Neurological disease	3.27	1.4 – 7.8	<.001
Prematurity	7.87	3.2 – 19.6	.007

Note: Variables in the equations: infant or not (age <2 years of age); sex; prematurity (gestational age <37 weeks); asthma; obesity; any neurological disease; allergic diseases (other than asthma).

COVID-19 score was associated with asthma, prematurity, neurological disease, and age <2 years of age. Age <2 years, prematurity, and neurological disease were significantly associated with hospitalization (Table 2).

Our results show that the morbidity of COVID-19 in children attending an ER should not be overlooked. Although most cases were mild, 14% of children in our study required hospitalization, including 5% in the ICU.

LRT involvement is considered a sign of severity during COVID-19 infection,[4] and it was observed in 14% of our cases. The relative infrequency in which wheezing was observed (4.8%) is noteworthy, even among children with asthma (19.4%).

Several hospitals have reported a significant decrease in cases of wheezing and/or exacerbation of asthma during the pandemic.[6,7] This reduction may be mainly due to the suspension of face-to-face school classes and social distancing measures, resulting in lower rates of viral infections. Even so, this relatively low tendency to induce viral wheezing by SARS-CoV-2 may have contributed to this scenario.

As observed in other respiratory viral infections, LRT involvement during COVID-19 was more common among children with asthma. Additionally, children with asthma had worse COVID-19 severity scores indicating that asthma may be a risk factor for more severe forms of COVID-19 among children seeking ER care. Nevertheless, we found no higher risk of hospitalization for COVID-19 among children with asthma. Insufficient sample size could be an explanation for this absence of association, since hospitalization was infrequent among children with COVID-19.

In adults, asthma is not associated with higher COVID-19 severity or worse outcomes (death, intubation, or mechanical ventilation).[8] In children, a systematic review of the literature published in the first semester of 2020 could not reach conclusions regarding the association of asthma and COVID-19 severity once information on the presence of asthma was present in only two case series of COVID-19.[9] Only a few other studies have addressed the relationship

between asthma and COVID-19 in children. Chao et al reported data from 46 children admitted due to COVID-19 in a New York hospital (13 in ICU). Asthma was a frequent comorbidity (24%) but was not associated with need for intensive care treatment.[2] Factors associated with hospitalization were not evaluated in this study. In Spain, Ruano et al described clinical data from 29 allergic asthmatic children with probable COVID-19. All children had mild symptoms of COVID-19, and mild bronchospasm was observed in 24% of them.[10] A European survey to 174 centers identified 49 asthmatic children with COVID-19 (51% in GINA steps 3 to 5). Of these, 67% were hospitalized (5 in ICU) and 19 needed oxygen supplementation, but only 20% presented with an asthma exacerbation.[11]

Chronic pulmonary disease and preexisting medical condition were identified as risk factors for ICU admission in the European multicenter study.[3] Asthma was the most frequent condition among these children (16 of 29) but was not studied independently. Preterm birth history and asthma were predictors for admission and for respiratory support in a retrospective cohort of 454 children with COVID-19 attended in a single hospital in Colorado, USA.[12]

In addition to the association between asthma and COVID-19, the present study may contribute to clarifying the role of other comorbidities or conditions in SARS-CoV-2 infections in children. However, the study has several limitations. Data were retrospectively collected from medical forms and records obtained during ER care, and there may be inaccuracies and omissions. Data on the clinical progress of non-hospitalized children may be incomplete in cases in which medical care was sought in another hospital. The presence of a medical diagnosis of asthma was recorded according to family information, and there may be inaccuracies. In addition, the diagnosis of asthma in young children is difficult to establish accurately and 51% of the children with asthma or recurrent wheezing in our study were ≤5 years of age. Thus, the interpretation of the findings should consider this limitation.

In conclusion, we have found that LRT involvement occurs in approximately 1/7 of children with COVID-19 presenting to the ER, but wheezing was infrequently observed. Asthma/recurrent wheezing and prematurity were associated with LRT involvement and worse COVID-19 severity scores among children seeking ER care.

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CONFLICT OF INTEREST

None of the authors have any conflicts of interest directly related to this work. Anna C. Rabha, Fátima R. Fernandes, and Dirceu Solé do not declare any conflicts of interest outside the submitted work. Leonard B. Bacharier reports personal fees from Aerocrine, GlaxoSmithKline, Genentech/Novartis, Merck, DBV Technologies, Teva, Boehringer Ingelheim, AstraZeneca, WebMD/Medscape, Sanofi/Regeneron, Vectura, and Circassia outside the submitted work. Gustavo F. Wandalsen reports personal fees from AstraZeneca, Merck Sharp & Dhome, Glenmark, and Mylan outside the submitted work.

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Anna Clara Rabha: Conceptualization (equal); Data curation (equal); Formal analysis (equal); Funding acquisition (equal); Investigation (equal); Methodology (equal); Writing-original draft (equal); Writing-review & editing (equal). **Fátima Rodrigues Fernandes:** Conceptualization (equal); Data curation (equal); Investigation (equal); Methodology (equal); Project administration (equal); Resources (equal); Validation (equal); Writing-review & editing (equal). **Dirceu Solé:** Conceptualization (equal); Methodology (equal); Supervision (equal); Validation (equal); Writing-review & editing (equal). **Leonard Bacharier:** Conceptualization (equal); Supervision (equal); Validation (equal); Writing-original draft (equal); Writing-review & editing (equal). **Gustavo Falbo Wandalsen:** Conceptualization (equal); Data curation (equal); Formal analysis (equal); Investigation (equal); Methodology (equal); Project administration (equal); Resources (equal); Supervision (equal); Validation (equal); Writing-original draft (equal); Writing-review & editing (equal).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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Food allergic reactions during the Covid-19 pandemic lockdown in Israeli children

To the Editor,

Coronavirus disease 2019 (COVID-19), the disease caused by severe acute respiratory syndrome coronavirus 2, has affected Israel along with most other nations during the current global pandemic. On March 19, 2020, a national state of emergency and lockdown was declared.[1] These events led to an extremely unusual situation in which children stayed only at home, with their primary caregiver. Therefore, we aim to determine the incidence, risk factors for food allergic reaction (FAR) and parental willingness to seek medical treatment during the COVID-19 pandemic lockdown compared to the preceding 3 months. An online questionnaire was developed by the authors using the Google drive application. The questionnaire comprised 32 items (Appendix S1) eliciting data about the food allergy (FA) diagnosis, number and nature of FARs before and during the lockdown period, allergy treatment availability and follow-up. The survey began on April 19, 2020 and ended on May 21, 2020. The definition of a FAR was based on the symptoms characterization of the Food Allergy and anaphylaxis Emergency Care Plan (FARE).[2] Notably, this document is endorsed by the Israel Association of Allergy and Clinical Immunology, and distributed to every patient. A link to the questionnaire was posted on the website of Israel Food Allergy Support Network (YAHEL). A total of 701 questionnaires were completed. Only patients diagnosed with IgE mediated FA by an allergist were included in the study. Fifty-six questionnaires were excluded (25- not diagnosed by allergist, 23-born in 2020, 6-OIT, 1-non-IgE allergy, 1-idiopathic anaphylaxis). Thus, the study included 645 children with FA (65.3% male; age 5.9 ± 3.7 years, range 0.3-18.5 years). Of these, 395 (61.2%)